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Exploring relapse through a network analysis of residual depression and anxiety symptoms after cognitive behavioural therapy: A proof-of-concept study

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Abstract

Objective: Many patients relapse within one year of completing effective cognitive behavioural therapy (CBT) for depression and anxiety. Residual symptoms at treatment completion have been demonstrated to predict relapse, and so this study used network analyses to improve specificity regarding which residual anxiety and depression symptoms predict relapse.

Method: A cohort study identified relapse cases following low- and high-intensity CBT in a stepped care psychological therapy service. The sample included N=867 'recovered' treatment completers that attended a six-month follow-up review. At follow-up, N=93 patients had relapsed and N=774 remained in-remission. Networks of final treatment session depression (PHQ-9) and anxiety (GAD-7) symptoms were estimated for both sub-groups.

Results: Qualitatively similar symptom networks were found. Difficulty concentrating was a highly central symptom in the relapse network, whilst of only average centrality in the remission network. In contrast, trouble relaxing was highly central in the remission network, whilst of only average centrality in the relapse network.

Discussion: Identification of central residual symptoms holds promise in improving the specificity of prognostic models and the design of evidence-based relapse prevention strategies. The small sample of relapse cases limits this study's ability to draw firm conclusions.

Keywords: Depression; Anxiety; Relapse; Network Analysis; Cognitive Behavior Therapy

Introduction

Depression and anxiety disorders are associated with high rates of relapse (< 12 months) and recurrence (≥12 months) after treatment (Bockting, Hollon, Jarrett, Kuyken & Dobson, 2015; Bruce et al., 2005; Burcusa & Iacono, 2007; Hardeveld, Spijker, De Graaf, Nolen & Beekman, 2010; Vervliet, Craske & Hermans, 2013). Cognitive behavioural therapy (CBT) is an effective acute-phase intervention (i.e. the period in which patients are actively experiencing a clinically significant problem; Kupfer, 1991) for depression and anxiety problems, and it has been shown to produce lower relapse rates compared to pharmacotherapy (Cuijpers et al., 2013; Hollon, Stewart & Strunk, 2006; Otto, Smits & Reese, 2005; Vittengl, Clark, Dunn & Jarrett, 2007). Despite this, many patients with apparently successful outcomes relapse quickly after completing either high- or low-intensity CBT. For example, a meta-analysis found that 29% of patients relapse within one year of high-intensity CBT, and this increases to 54% within two years if recurrence events are also considered (Vittengl et al., 2007). In low-intensity CBT (i.e. brief guided self-help), 53% of patients with remission of symptoms were found to relapse within one year, with a further 13% experiencing a recurrence within two years (Ali et al., 2017; Delgadillo et al., 2018). These findings suggest that treatment gains for some patients are not sustained following CBT, which raises a need to better understand how to improve the longer-term benefits of therapy.

Residual symptoms at the end of CBT treatment have been found to predict relapse (see meta-analysis by Wojnarowski, Firth, Finegan, & Delgadillo, 2019). The level of residual symptoms is typically estimated with sum-scores of standardized outcome measures computed across a set of individual symptom scores (Fried & Nesse, 2015b). Calculating sum-scores in this manner presupposes that symptoms develop from a common cause and that all the symptoms of a disorder are interchangeable and equally important indicators of

severity. However, there are reasons to question these assumptions (Fried & Nesse, 2015b). For example, it has been argued that there are approximately 1000 unique symptom profiles that all meet the criteria for a diagnosis of major depression according to the DSM-5 (APA, 2013) definition (Fried & Nesse, 2015a). Moreover, the typical sum-score approach is usually based on a reflective measurement model that regards observed variables (such as item scores) as emanating from a common underlying latent construct. From this standpoint, individual symptoms do not directly interact but are rather assumed to be statistically independent when their common underlying cause is taken into account. This assumption is frequently at odds with clinical experience in that at least some symptoms (e.g. insomnia) are reported to have causal relationships with other symptoms (e.g. fatigue; Ferentinos et al., 2009; Fried & Nesse, 2015b).

Using sum-scores to aggregate across variables that may be functionally related may obscure potentially important individual differences in patterns of contingencies between symptoms that may represent relapse signatures (i.e. processes, factors and choices that signal the risk of imminent relapse). The identification of such key symptom interactions could better support the investigation of theories such as the 'kindling' approach to relapse in depression (Stroud, Davila & Moyer, 2008).

The network approach to psychopathology (Borsboom & Cramer, 2013) was developed as an alternative to the standard measurement approach in the field based on latent variables and sum scores. Notably, networks accommodate the possibility of local interactions between variables measured by individual scale indicators. Network models consist of nodes (i.e. items on measures representing specific symptoms) and edges (i.e., the connections between nodes). According to the network approach, symptom covariance is not assumed to stem from a common cause, but rather reflects that symptoms are connected in a dynamic network of direct and indirect causal interactions. One symptom can trigger a causal

chain involving other symptoms being reciprocally elicited and vicious cycles to be established that patients find hard to break or alter (e.g. insomnia → concentration problems → worthlessness → depressed mood → insomnia). Such feedback loops within symptom networks result in symptoms co-evolving and becoming self-sustaining, potentially resulting in a characteristic pattern of symptoms that create a diagnosable mental disorder (Borsboom, 2017).

There has been a significant increase in clinical research adopting the network approach within the last decade (see Fried et al., 2017, for a review). For example, in relation to studying remission, von Borkulo et al. (2015) explored N= 515 patients who were experiencing at least moderate depressive symptoms, and who had been diagnosed with depression in the previous 12 months. Baseline symptom networks (11 symptoms) were compared between patients still suffering from depression two years after baseline (i.e. 'persisters'; N=253), and those who had recovered after two years (i.e. 'remitters'; N= 262). At baseline, in the persisters' network, symptoms were significantly more connected (i.e. correlated with each other) than the remitters' network. In particular, symptoms of 'fatigue' and 'guilt' were more central (i.e. more correlated with other symptoms) in the persisters' network than in the remitters' network. This study illustrates the potential usefulness of the network approach in its ability to explore numerous symptoms and their interrelationships - a fundamental challenge of psychotherapy research - and its potential for generating testable hypotheses related to these variables. There are no alternative analytic strategies available at present to our knowledge that offer comparable capabilities.

This exploratory, 'proof-of-concept' study applied a network approach to investigate the role of residual symptoms in predicting relapse of depression and anxiety following CBT. Network analyses were conducted to compare the symptom network structures of cases that did and did not experience a relapse of depression and/or anxiety symptoms within six

months of completing low- and high-intensity forms of CBT. These analyses aimed to identify specific symptoms that may be highly connected in the relapse network, but not as connected to the same degree in the remitters network. This would therefore highlight symptoms that potentially play a role in relapse. Identifying such symptoms could provide valuable targets for relapse prevention interventions applied during the acute-phase of treatment and then applied by patients thereafter.

Method

Design and Setting

This study analysed data previously collected for a naturalistic, prospective cohort study conducted by Wojnarowski, Kellett, Sainty and Delgadillo (under review). This data was collected from a single psychological therapy service in the north of England within the Improving Access to Psychological Therapies programme (Clark, 2011). The study had ethical approval from an independent Research Ethics Committee and the NHS Health Research Authority (Ref: 17/WA/0063). IAPT uses a 'stepped care' service delivery system that implements National Institute for Health and Clinical Excellence (NICE; 2011) guidelines for the treatment of depression and anxiety (Clark, 2011). In stepped care, patients are initially offered low-intensity guided self-help interventions, and if patients do not respond to this initial step they are subsequently offered high-intensity psychological interventions. The first-line treatments within IAPT are CBT-based low and high intensity interventions, however other high intensity interventions (e.g. interpersonal therapy) are also offered. Low-intensity CBT in this service was highly standardized, brief (< eight sessions), psycho-educational support offered by qualified psychological wellbeing practitioners trained to a national curriculum and in receipt of weekly case management supervision driven by outcome monitoring (National IAPT Team, 2015). High-intensity CBT (up to 20 sessions) was delivered by qualified and

accredited cognitive behavioural psychotherapists following disorder-specific and protocol-driven CBT models recommended in the CBT for anxiety and depression competency framework (Roth & Pilling, 2008).

The service involved in this study started routinely offering follow-up review appointments to patients who successfully completed treatment (i.e. achieved remission of symptoms by the end of treatment) in 2013; data collection for this study began in 2013 and ended in 2015. The follow-up appointments were conducted by the same therapists that delivered treatment. Reviews took place within six months of this final session, however the exact timing was negotiated between therapist and client to occur at a mutually agreeable time. As the timing of follow-up appointments was therefore flexible, there was significant variability in follow-up durations. This period ranged from one-to-six months, with the modal duration being four months (for approximately 60% of cases). Only data for cases in which the follow-up review occurred at least three months after the final treatment session were analysed. There were two reasons behind this approach. First, in some cases in which the timing between the final treatment session and follow-up review was shorter (e.g. one month), this length of time was not significantly different from the length of time between acute-phase treatment sessions. Furthermore, these cases were extreme outliers among the wider distribution. Second, in clinical trials, three months is frequently used as a short-term follow-up.

Participants

Participants were a subsample of cases from the cohort studied by Wojnarowski et al. (under review). The sample included data for N=867 patients, of whom N=93 (11%) were "relapsed cases" and N=774 (89%) were classed as "in remission". This was a subset of a wider cohort (N=2899) of patients who completed low- and high-intensity CBT with full

remission of depression and anxiety symptoms. The subset used in the present study included only cases that attended scheduled follow-up review appointments to determine relapse status. Of the wider cohort, N=1348 patients were offered a follow-up review, with N=968 attending. As this study only analysed data for cases in which the follow-up review occurred at least three months following treatment completion, N=868 of the N=968 cases were eligible for analysis. One of these cases had missing item-level data for the PHQ-9 and GAD-7 for the final treatment session, meaning they could not be included in the network analyses. This resulted in the final sample of N=867 patients. Further details about the wider cohort are reported by Wojnarowski et al. (under review).

Fourteen different primary mental health problems were recorded for patients included in this study sample, with the three most common being: mixed anxiety and depression (40.7%); depressive episode (18%); and generalised anxiety disorder (15.8%). Within the included sample: 33% were male; the mean age at referral was 44 (SD = 16.3); 99% were white British; 11% were unemployed; and 67% received high-intensity CBT, while 33% received low-intensity CBT. Table 1 contains the demographic information and mean outcome scores from different time points of the relapse and remission subsamples.

Primary Outcome Measures

Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer & Williams, 2001): A nine-item screening tool for major depression based on the symptoms listed in the DSM-5 (Table 2). Each item assesses the frequency that patients experience a specific symptom over a period of two weeks on a scale ranging from 0-3 (i.e. ‘not at all’ to ‘nearly every day’). The maximum score that can be obtained for this measure is 27, and the recommended diagnostic cut-off criteria for major depression is a score of 10 (NHS, 2018). The Cronbach’s alpha for the PHQ-9 in this study’s sample was 0.84.

Generalized Anxiety Disorder scale (GAD-7; Spitzer, Kroenke, Williams & Lowe, 2006): A seven-item screening tool for anxiety disorders (Table 2). Similar to the PHQ-9, each item assesses the frequency that specific anxiety symptoms are experienced over a period of two weeks, and the same scale as the PHQ-9 (i.e. 0-3) is used. The maximum score that can be obtained from the GAD-7 is 21, and the recommended cut-off for the detection of an anxiety disorder is a score of 8 (NHS, 2018). The Cronbach's alpha for the GAD-7 in this study's sample was 0.83.

In order to assess reliable change in the above measures as part of routine outcome monitoring, Richards and Borglin (2011) proposed reliable change indices of ≥6 for PHQ-9 and ≥5 for GAD-7.

These self-administered outcome measures are collected at every session in IAPT services to monitor a patient's response to treatment (Clark, 2011). Table 2 contains the item numbers and associated symptoms for the PHQ-9 and the GAD-7. Scores from these measures from three different time points were analysed in this study: 1) baseline scores from the initial assessment; 2) scores from the final acute-phase treatment session; and 3) scores from follow-up review appointments.

Relapse was defined following the method proposed by Delgadillo et al. (2018). Three criteria had to be met for a patient to be classed as having relapsed: a) their PHQ-9 and GAD-7 scores from the final session were below the respective measures' diagnostic cut-off criteria; b) at least one of their PHQ-9 or GAD-7 scores was above the cut-offs at the follow-up review; and c) any outcome score at follow-up that was above the cut-off also displayed statistically reliable deterioration (i.e. an increase greater or equal to the reliable change index) in comparison to the final treatment session. Patients with an outcome measure score

above the diagnostic cut-off at follow-up, which did not display clinically significant deterioration, were classed as remaining in-remission.

Network Estimations

First, network structures of baseline PHQ-9 and GAD-7 symptoms were estimated separately for relapse and remission samples. From the study subsamples of N=93 relapsed patients and N=774 patients in remission, two relapsed patients and five remitted patients did not have available baseline item-level data. Therefore, a baseline symptom network model was estimated using data from N=91 relapsed patients, while another network model was estimated using data from N=769 remitted patients. These networks were qualitatively compared to explore whether there were differences in terms of symptom profiles at the beginning of treatment. Following this, network structures of symptoms displayed at the final treatment session were also estimated separately for the total relapse and remission samples.

Network models were estimated using the R package qgraph (Epskamp, Cramer, Waldorp, Schmittmann & Borsboom, 2012). When using qgraph, the settings were customised to display red edges to represent negative partial correlations, and green edges to represent positive partial correlations. Stronger partial correlations are represented by more saturated and wider edges. The edges were estimated using regularized partial correlations between symptoms. The calculation of partial, rather than zero-order, correlations meant that edges present in a network represent relationships between two nodes when the influence of all other nodes in the network was controlled (Epskamp & Fried, 2018). Each network was initially estimated using partial polychoric correlations, which is a technique of correlation estimation that can be used for ordinal variables. Polychoric correlations are calculated by estimating the correlation between two unobserved but theorised normally distributed continuous variables that are assumed to underlie observed ordinal variables (Salkind, 2010).

Following the estimation of networks based on partial polychoric correlations, we then re-estimated each network based on partial Spearman correlations. Epskamp and Fried (2018) recommend this procedure so that networks derived from both types of correlation matrices can be compared. If they do not appear to be similar, this indicates potential artefacts arising from the estimation of polychoric correlations and consequently casts doubt on the resulting network structure, thus suggesting that Spearman correlation networks should be used.

As the production of networks involves the estimation of a significant number of parameters (i.e. 136 parameters for a network containing 16 nodes; Beard et al., 2016), it is likely that some false-positive edges are produced. The network models were therefore regularized by applying the graphical LASSO (i.e. Least Absolute Shrinkage and Selection Operator) algorithm to eliminate likely false-positive edges from the estimated networks (Friedman, Hastie & Tibshirani, 2008). Application of the Graphical LASSO algorithm thus produces a sparse, more conservative network containing the smallest number of edges needed to explain the covariance of nodes.

The R package qgraph (Epskamp et al., 2012) automatically applies the graphical LASSO algorithm in combination with Extended Bayesian Information Criterion (EBIC; Chen & Chen, 2008) model selection. The EBIC encompasses a hyperparameter γ (gamma), which is set manually by the researcher, that determines to what degree simpler models (fewer edges) should be preferred by the EBIC. The hyperparameter is typically set between 0 and 0.5, with higher values indicating a preference for simpler, more conservative models (Epskamp & Fried, 2018). Due to this study's exploratory nature, γ was set to 0 for all estimated networks to err on the side of discovery.[1]

[1] When γ=0.5 the estimated network for the relapse sample contained only six edges. The estimated network for the remission sample was highly similar to the one estimated when γ=0.

To assist with comparisons between symptom networks at the final treatment session of subsequent relapse and remission samples, three indices of node centrality were calculated to identify the most central symptoms of the network (McNally, 2016). For each node, the centrality indices calculated were: strength, which denotes the absolute sum of edge weights (i.e. correlation coefficients) connected to a node; betweenness, which represents the number of times a node is present on the shortest path between two other nodes; and closeness, which signifies the average distance from one node to other nodes in the network. Differences in central symptoms at the final treatment session between remission and relapse samples could indicate symptoms associated with relapse.

Network Stability

Finally, the stability of each estimated network was assessed in two stages. First, to assess the stability of network edges, a bootstrap approach was adopted to calculate 95% confidence intervals for edge values. Second, to assess the stability of a network's centrality indices, a case-dropping bootstrap was performed. In this process, the centrality measures derived from the complete dataset were repeatedly correlated with centrality measures derived from a subsample that had a percentage (e.g. 10% or 40%) of participants or nodes missing. If correlation coefficients decrease significantly as nodes or participants are removed, the centrality measure is considered unstable. The results of the case-dropping bootstrap can be summarized in a coefficient called the correlation stability coefficient (CS-coefficient), which should be at least 0.25 for a centrality index to be considered stable, but should ideally be above 0.5. Both stages of stability assessments were completed using the R package bootnet (Epskamp, Borsboom & Fried, 2017).

Results

Preliminary Analysis

Comparisons of the patient characteristics of the relapse and remission samples found no significant differences in terms of gender, ethnicity, employment status, and age respectively (all $p > .05$). However, a significant association was found between the intensity of treatment and whether a patient relapsed or not ($\chi^2(1, N = 867) = 5.31$, $p = .004$, $\varphi = .08$); a higher proportion of relapsed patients (77%) received high-intensity CBT than remitted patients (66%). In addition, the relapse sample ($M = 3.98$; $SD = 2.65$) had significantly higher PHQ-9 scores at the end of treatment ($t(865) = -2.80$; $p = .005$) than the remission sample ($M = 3.20$; $SD = 2.54$). Similarly, the relapse sample ($M = 3.52$; $SD = 2.19$) also had significantly higher GAD-7 scores at treatment completion ($t(865) = -2.72$; $p = .007$) than the remission sample ($M = 2.89$; $SD = 2.08$).

Network Differences at Baseline

The networks of baseline symptoms based on polychoric correlations and the same networks based on Spearman's correlations did not appear to substantially differ in appearance (see Supplementary Materials A for comparisons). The networks based on Spearman's correlations were determined to be the most appropriate for baseline data, as these had higher stability compared to networks based on polychoric correlations. These networks were therefore examined in subsequent analyses.

Figure 1 illustrates that the symptom network for the relapse sample (panel a) was highly similar to the symptom network for the remission sample (panel b) at the initial (baseline) assessment. Both networks appeared to have two distinct clusters of symptoms, with PHQ-9 symptoms primarily being more related with each other, and a similar pattern occurring with GAD-7 symptoms. The only moderately strong association existing between a

PHQ-9 symptom and a GAD-7 symptom for both networks was found to be between "psychomotor agitation/deficits" (Motor) and "restlessness" (Restless).

Network Differences at Final Treatment Session

The networks of symptoms from the final treatment session based on polychoric correlations were substantially different from the same symptom networks based on Spearman's correlations (see Supplementary Materials B for comparisons). These dissimilarities, along with the polychoric correlation networks being densely connected and including many unexpected negative edges, indicated that the polychoric correlations were untrustworthy (Epskamp & Fried, 2018). Therefore, networks based on Spearman's correlations were deemed to be the most appropriate for symptoms from the final treatment session, and these networks were therefore examined and interpreted.

Figure 2 suggests that the symptom network for the final treatment sessions for the relapse sample (panel a) had substantially less connectivity than the symptom network for the remission sample (panel b). However, the lack of edges represented in the relapse network is likely explained by the relapse sample being too small, as networks based on small sample sizes have often been found to contain fewer edges (Epskamp & Fried, 2018). Indeed, regularization shrinks edges more if there is a small sample size to avoid false positives.

The edges present in the relapse network were also present in the remission network, indicating that the networks were fairly similar. However, two of the strongest associations present in the remission network failed to appear (even as weak associations) in the relapse network. These associations were between: "psychomotor agitation/deficits" (Motor) and "restlessness" (Restless); and "trouble sleeping" (Sleep) and "trouble relaxing" (Relax).

Strength was the only centrality index that was estimated to have sufficient stability for both the relapse network (CS(cor=0.7) ≈ 0.366) and the remission network (CS(cor=0.7) ≈

0.749). Therefore, this is the only centrality measure that will be discussed here (see Table 3). The strength measures for both networks were highly similar, with many symptoms having relatively similar level of centrality within the networks. However, two symptoms had highly contrasting levels of centrality. “Trouble relaxing” (Relax; an anxiety symptom), was the most central node in the remission network, but only the eighth most central node in the relapse network. Meanwhile, “trouble concentrating” (Concent; a depression symptom) was the second most central node in the relapse network while being only the eighth most central node in the remission network.

Network Stability

Bootstrapped 95% confidence intervals revealed the two estimated networks for the remission sample (i.e. symptoms at 1) baseline and 2) final treatment session) to be somewhat stable. However, the two estimated symptom networks for the relapse sample were unstable.

Discussion

This is the first study to apply network analysis to examine the symptom structure of relapse versus remission cases following routinely delivered CBT. Consistent with available evidence (Wojnarowski et al., 2019), this study demonstrated that patients who relapse have significantly higher levels of residual depression and anxiety symptoms at the final treatment session. This suggests that residual symptoms are not minor issues to be ignored by clinicians or noise in the psychometric measure, but rather an important prognostic indicator that a patient remains psychologically vulnerable and is therefore at potential risk of relapse.

The pre-treatment symptom networks appeared to have highly similar structures. Both networks exhibited two distinct clusters of symptoms, with one cluster consisting of PHQ-9 symptoms and the other cluster consisting of GAD-7 symptoms. This illustrates that at baseline, individual symptoms of depression and anxiety conformed to the expected factor

structures of affective and anxiety symptoms. The high similarity between the two baseline symptom networks indicates that patients that go onto relapse or remain in remission appear to have similar symptom profiles at the start of treatment.

The relapse network based on symptoms assessed at the final treatment session contained relatively fewer edges, despite the EBIC hyperparameter γ being set to 0 (consistent with a less restrictive model), which was a significant limitation and likely due to the small sample size (Epskamp & Fried, 2018). Inadequate sample sizes often lead to networks with relatively fewer edges as a consequence of regularization, which penalizes edge weights more when the sample is underpowered to avoid false positive associations. This process operates well when the "true" network is sparse, but there is a risk, when using small samples, of regularization returning a sparse network when the "true" network is not sparse. Epskamp, Kruis and Marsman (2017) describe a general rule of having at least as many observations as estimated network parameters (136 in this study), but they explain that this general rule also sometimes results in unstable estimates. Therefore, there are currently no clear guidelines on the required sample for stable network estimations.

The fact that sparse networks were not produced for the relapse sample at baseline may potentially be explained by the relatively restricted range of symptom scores at the end of treatment (below the diagnostic threshold). This did not occur at baseline for the relapse sample when symptom scores had a broader range and greater variance (see Supplementary Materials C).

For the most part, the same edges were present in the remission and relapse networks and largely the same items were central in both networks, indicating that both networks were highly similar. However, some noticeable differences between the two networks were observed. First, two of the strongest edges (between 'psychomotor agitation/deficits' and

‘restless’, and between ‘disrupted sleep’ and ‘trouble relaxing’) present in the remission network were not present, even as weak associations, in the relapse network and despite other edges being present in the network. Second, two symptoms had highly contrasting levels of centrality within the two networks. One of these symptoms was ‘trouble concentrating’, which was the second most central symptom in the relapse network, while being only the eighth most central symptom in the remission network. Meanwhile, ‘trouble relaxing’ was the most central symptom in the remission network, and only the eighth most central symptom in the relapse network.

The prominent centrality of ‘trouble concentrating’ within the relapse network may suggest that activation of this symptom has stronger exacerbating effects on other symptoms for patients vulnerable to relapse, while activation does not possess these effects for patients that are less vulnerable to relapse. This may therefore indicate that ‘trouble concentrating’ is an important predictor of relapse, and potentially a worthwhile target for relapse prevention interventions. This suggests that on completion of apparently successful CBT, clinicians could routinely inquire about concentration difficulties. Indeed, Boschloo, van Borkulo, Borsboom, and Schoevers (2016) found that the four most central symptoms of depression in a non-clinical sample were most predictive of who would later develop depression, illustrating the potential predictive power of central symptoms.

Meanwhile, it is more difficult to interpret the finding that ‘trouble relaxing’ was the most central symptom in the remission network, while only possessing average centrality in the relapse network. It is possible that this was a false positive, and more research is needed to interpret this finding if indeed it should be replicated by others. Moreover, although a number of studies have confirmed the role of central symptoms as predictors and targets of treatment, other studies have shown these not to be superior predictors to simple sums and counts of symptoms (e.g. Rodebaugh et al., 2018). Additionally, a more fundamental critique

has recently appeared questioning the interpretation of centrality as representing causal influence between psychological phenomena (Bringmann et al, 2018).

One potential approach to better test the centrality of depressive and anxious symptoms in predicting relapse, is to conduct a prospective study involving ecological momentary assessment (EMA) methods and associated dynamic network modelling (see Lutz et al., 2018, for an example application of this method). EMA enables an intensive real-time, within-subjects repeated assessment of a patient's current thoughts, feelings and behaviours, typically collected using a mobile device (e.g. smartphone). The dynamic network model approach can then consider how symptoms interact and change over time within individuals to predict relapse (e.g. multilevel vector autoregressive models; mlVAR; Bringmann et al., 2013). This approach enables the individual and temporal dynamics of patient symptoms to be explored, thus allowing for idiographic explorations. The mlVAR modelling of EMA data enables a dynamic symptom network to be estimated for each individual patient within a sample, and consequently the centrality measures of specific symptoms for each individual patient can then be extracted. This allows for predictive models including these centrality measures to be tested, allowing for the investigation of network metrics as potential predictors of relapse.

To date, sum-scores of residual symptoms have been the most well-established predictor of relapse. The findings of this study's network analysis may indicate that concentration deficits may play a unique role in the risk of relapse, and that this signal may have been obscured in studies that use sum-scores. However, this needs further replication and the use of EMA methods could help to establish if this signal is reliable and adds enhanced predictive or clinical value over and above the parsimonious risk factor of residual symptom sum-scores.

Limitations

It is important to consider that this study's findings were reached through a qualitative comparison of symptom networks. Ideally, the symptom networks would have been compared using quantitative methods. One method to accomplish this would be to conduct a permutation test called the Network Comparison Test (NCT; (van Borkulo et al., 2017). An NCT was not conducted in this study due to: (1) the significant difference between the relapse and remission sample sizes violating an important assumption of the test (Epskamp & Fried, 2018); and (2) the lack of variance in symptom scores across both subgroups (see Supplementary Materials C), primarily caused by the predominance of "zero" scores. NCT analysis would require that further research exploring symptom network differences between relapse and remission samples are carried out using larger, similarly sized samples. The analysis of a larger and adequately powered sample would also allow for the networks to be estimated with the EBIC hyperparameter γ set to 0.5, thus allowing for more cautious and conservative models (i.e. less spurious edges included) to be produced. Considering these limitations, it is important for future research to replicate this study using larger samples.

However, the use of larger samples may not fully address the issue regarding the lack of variance in symptom scores. This floor effect (zero scores) would likely persist in studies with larger samples, given the nature of the time point at which data is collected (i.e. when patients attain remission of symptoms). Therefore, a "zero-inflated" NCT is required to allow for the test to be conducted in this context, but unfortunately this is not currently available.

Another limitation of this study is evidence of selection bias within the dataset. Previous analysis of the original sample found that patients with higher PHQ-9 scores at the final treatment session were less likely to be offered follow-up by therapists (Wojnarowski et al., under review). As residual symptoms appear to have a predictive role in relapse, it could

be assumed that many of the patients who were not offered follow-up relapsed. However, as these patients were not followed-up, their data could not be included in the present analysis.

This study was also limited by the brief, highly variable follow-up durations (between one and six months). These limitations, as well as the selection bias, likely explain the low base rate of relapse observed in this study (i.e. 11% compared to rates of 30% in controlled trials of CBT, and 53% in a naturalistic study of low-intensity CBT; Ali et al., 2017; Vittengl et al., 2007). Follow-up appointments offered to every patient, conducted in a structured manner and at a longer period after the completion of treatment would likely observe a more typical relapse base rate. Future research in this area should involve structured and longer term follow-up periods. The inclusion of structured and validated clinical interviews at follow-up would also provide greater confidence that relapse had occurred, particularly when combined with the use of validated outcome measures.

Finally, this study was unable to quantify variability in relapse rates that might be attributable to therapists, as data was not available regarding the therapists who provided treatment. It is also unclear what techniques would be available to estimate network models from a nested data structure. Nevertheless, an investigation into therapist effects of relapse would be an interesting direction for future research, particularly as therapist effects have been estimated to account for 6-7% of outcome variance for low-intensity CBT (Firth, Barkham, Kellett & Saxon, 2015).

Clinical Implications

The clinical implications of this study mainly relate to the need for (a) relapse prevention work being a valued and core component of treatment, (b) the offer of routine structured follow-up to identify patients at risk of relapse following treatment and (c) the potential for the provision of booster sessions that supplement structured follow-up.

Dynamic network modelling could prove important through the identification of central residual symptoms of depression and anxiety that improve the specificity of relapse prevention interventions. If such studies indeed identify certain symptoms or patterns to be significant predictors of relapse, this could help to guide post-treatment 'booster' interventions for patients. Risk of relapse needs to be normalised in patient psychoeducation, so that patients do not feel a 'failure' concerning relapsing, and avoid seeking further help due to feeling ashamed. Individuals who display the identified predictive symptoms can be identified as being 'at risk' by services, and subsequently targeted for offering booster sessions and bespoke relapse prevention strategies. This would support patients in maintaining their treatment gains, consequently removing their need for further intensive treatment which creates a 'revolving door' cycle in mental healthcare services.

Conclusion

The estimated network models indicated that relapse and remission cases have highly similar symptom profiles at the end of treatment, despite relapse cases having higher summed-scores in depression and anxiety measures. Nevertheless, certain differences emerged, such as concentration deficits possessing high centrality in the relapse sample, but only average centrality in the remission sample. However, this study was limited by an underpowered relapse sample. Interpretations should therefore be considered with caution, as they represent the first step in using network theory to predict relapse following routinely delivered low- and high-intensity CBT. Further research is necessary to replicate this study using adequately powered samples, so that more stable, accurate relapse symptom networks can be estimated. The adoption of EMA methods and associated dynamic network modelling should also be a focus of future research. The network approach holds promise in improving our understanding of the role of residual symptoms in predicting relapse, and thus potentially providing more specificity to evidence-based relapse prevention work.

Clinical or Methodological Significance Summary

This is the first study to adopt a network approach to explore residual levels of specific depression and anxiety symptoms and their role in relapse following cognitive behavioural therapy. Concentration deficits emerged as a highly central symptom in cases that relapsed. Such research may help in identifying specific symptoms that are predictive of relapse, and as a consequence potentially improve the specificity of relapse prevention interventions.

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Disclosure of Interest

The authors report no conflict of interest.

Data Availability Statement

In line with the requirements of the ethics review board for this study, requests for access to data are to be made in writing to the corresponding author.

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Table 1

Demographic Information and Mean Outcome Scores of Relapse and Remission Samples

	Relapse Sample	Remission Sample
N	93	774
Male	40%	32%
Mean Age (SD)	47 (17.2)	44 (16.2)
White British	99%	99%
Unemployed	17%	11%
Received High Intensity CBT At Treatment Completion	77%	66%
Received Low Intensity CBT At Treatment Completion	23%	35%
Mean PHQ-9 Score at Baseline	14.58	12.92
Mean GAD-7 Score at Baseline	13.28	12.60
Mean PHQ-9 Score at Final Treatment Session	3.98	3.20
Mean GAD-7 Score at Final Treatment Session	3.52	2.89
Mean PHQ_9 Score at Follow-Up Appointment	11.85	3.08
Mean GAD-7 Score at Follow-Up Appointment	11.10	2.89

Table 2

PHQ-9 and GAD-7 Items and their Corresponding Symptoms

Item	Symptom	Network Label
PHQ9_Q1	Low interest or pleasure	Anhedon
PHQ9_Q2	Feeling down, depressed or hopeless	Depress
PHQ9_Q3	Trouble sleeping	Sleep
PHQ9_Q4	Tired or little energy	Energy
PHQ9_Q5	Poor appetite/overeating	Appetite
PHQ9_Q6	Guilt	Guilt
PHQ9_Q7	Trouble concentrating	Concent
PHQ9_Q8	Psychomotor agitation/deficits	Motor
PHQ9_Q9	Suicidal thoughts	Suicide
GAD7_Q1	Nervous, anxious or on edge	Nervous
GAD7_Q2	Uncontrollable worry	ConWor
GAD7_Q3	Excessive worry about different things	ExcWor
GAD7_Q4	Trouble relaxing	Relax
GAD7_Q5	Restlessness	Restless
GAD7_Q6	Easily annoyed or irritated	Annoyed
GAD7_Q7	Afraid something awful might happen	Afraid

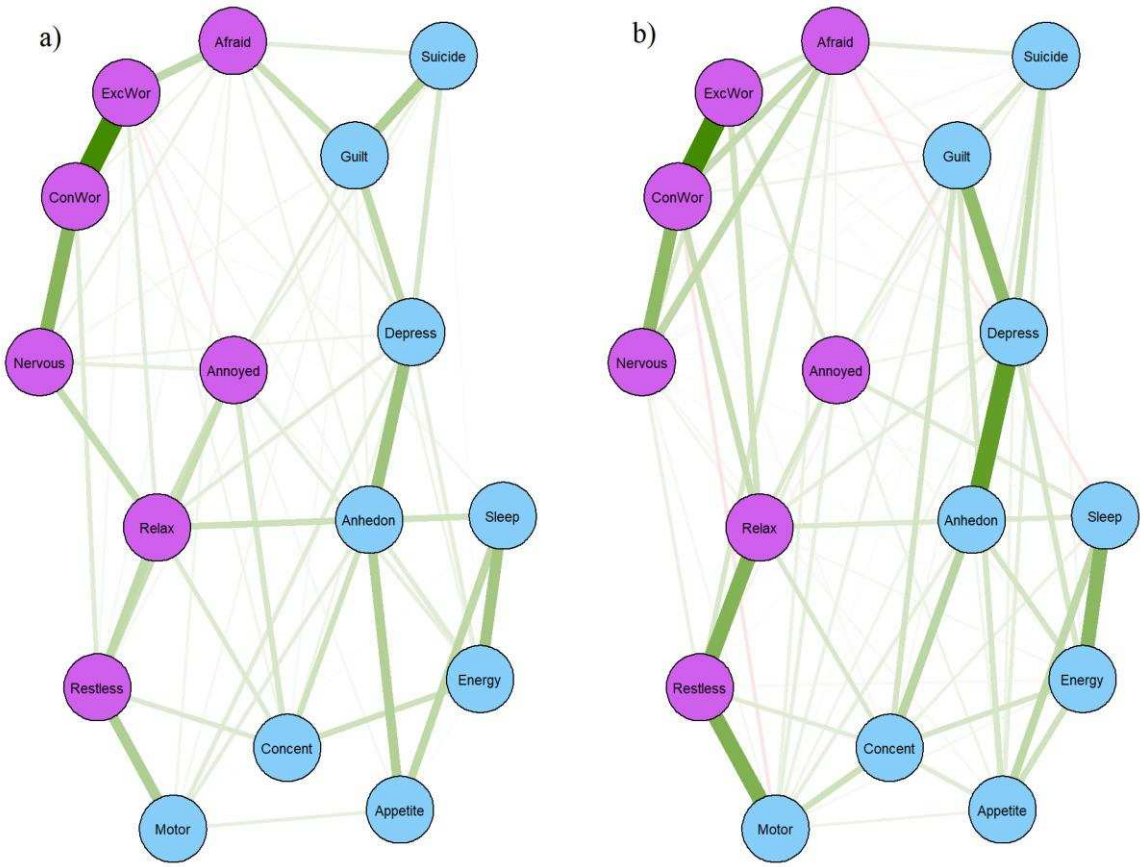

Figure 1. Network of baseline PHQ-9 (blue) and GAD-7 (purple) symptoms for a) the relapse sample and b) the remission sample.

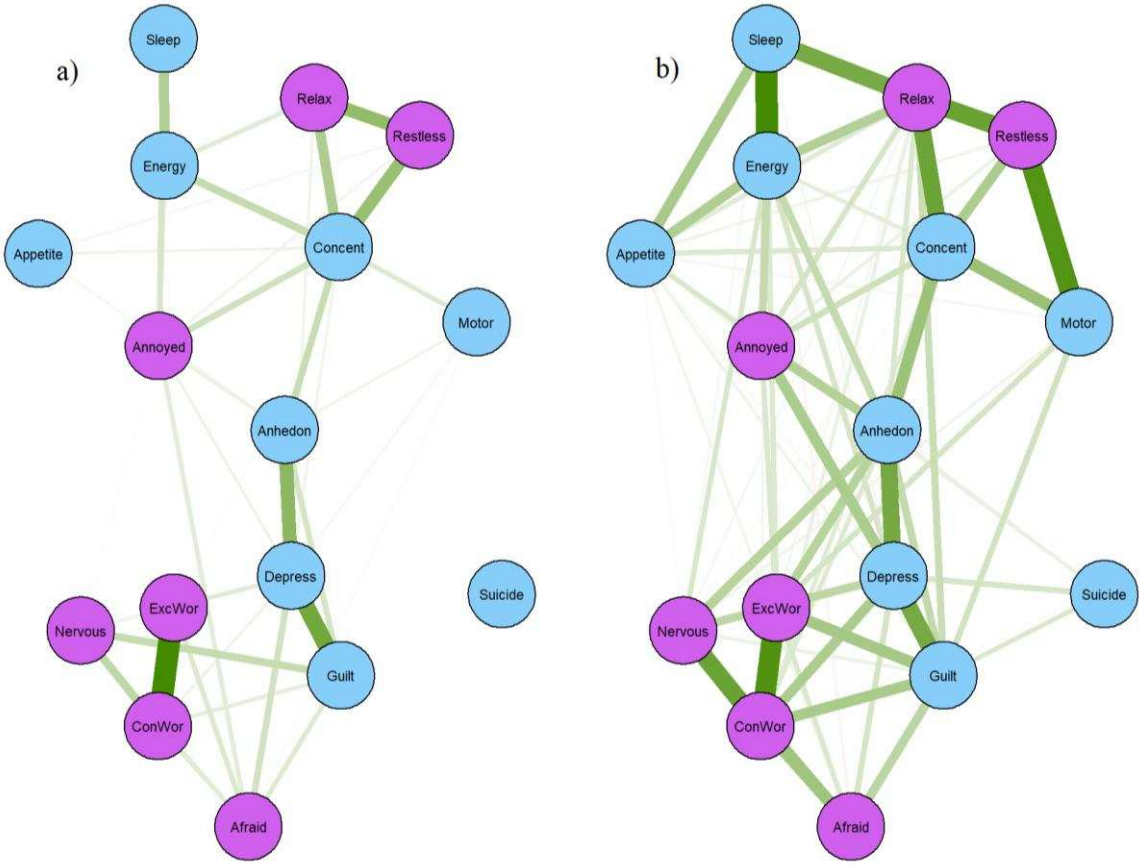

Figure 2. Network of PHQ-9 (blue) and GAD-7 (purple) symptoms at the final treatment session for a) the relapse sample and b) the remission sample.

Table 3

Ranked Strength Values for each Node in the Relapse and Remission Networks of Symptoms at the Final Treatment Session sorted by Rank Discrepancy

Symptom	Relapse Network Strength Rank (Strength Value)	Remission Network Strength Rank (Strength Value)	Strength Rank Discrepancy
Relax	8 (0.540)	1 (1.048)	7
Concent	2 (0.937)	8 (0.837)	6
Anhedon	6 (0.585)	2 (1.031)	4
Restless	7 (0.550)	11 (0.646)	4
Energy	10 (0.449)	6 (0.891)	4
Afraid	11 (0.445)	15 (0.511)	4
Depress	1 (0.959)	4 (0.979)	3
Annoyed	9 (0.450)	12 (0.627)	3
Nervous	12 (0.376)	9 (0.776)	3
Sleep	13 (0.274)	10 (0.751)	3
ExcWor	5 (0.610)	7 (0.861)	2
Guilt	4 (0.694)	5 (0.911)	1
Motor	14 (0.140)	13 (0.576)	1
Appetite	15 (0.081)	14 (0.537)	1
ConWor	3 (0.744)	3 (1.000)	0
Suicide	16 (0.000)	16 (0.175)	0

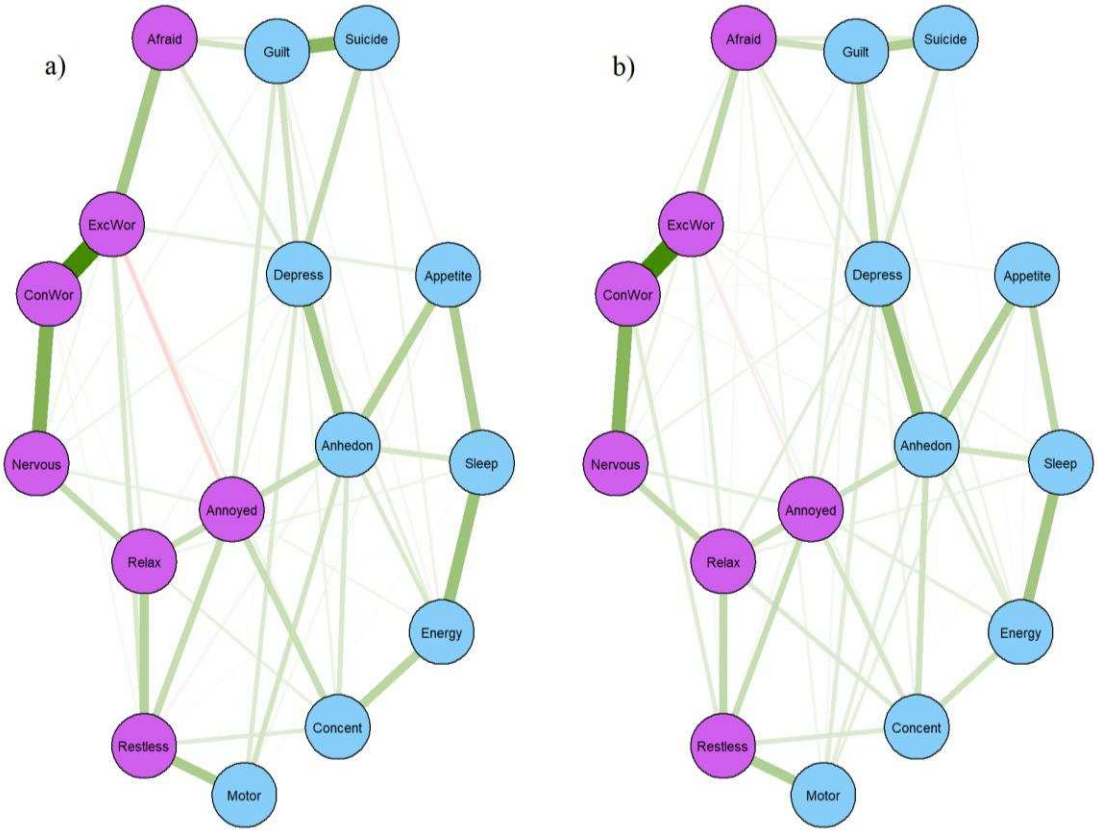

Figure A1. Network of baseline PHQ-9 (blue) and GAD-7 (purple) symptoms for the relapse sample using a) polychoric correlations and b) Spearman's correlations

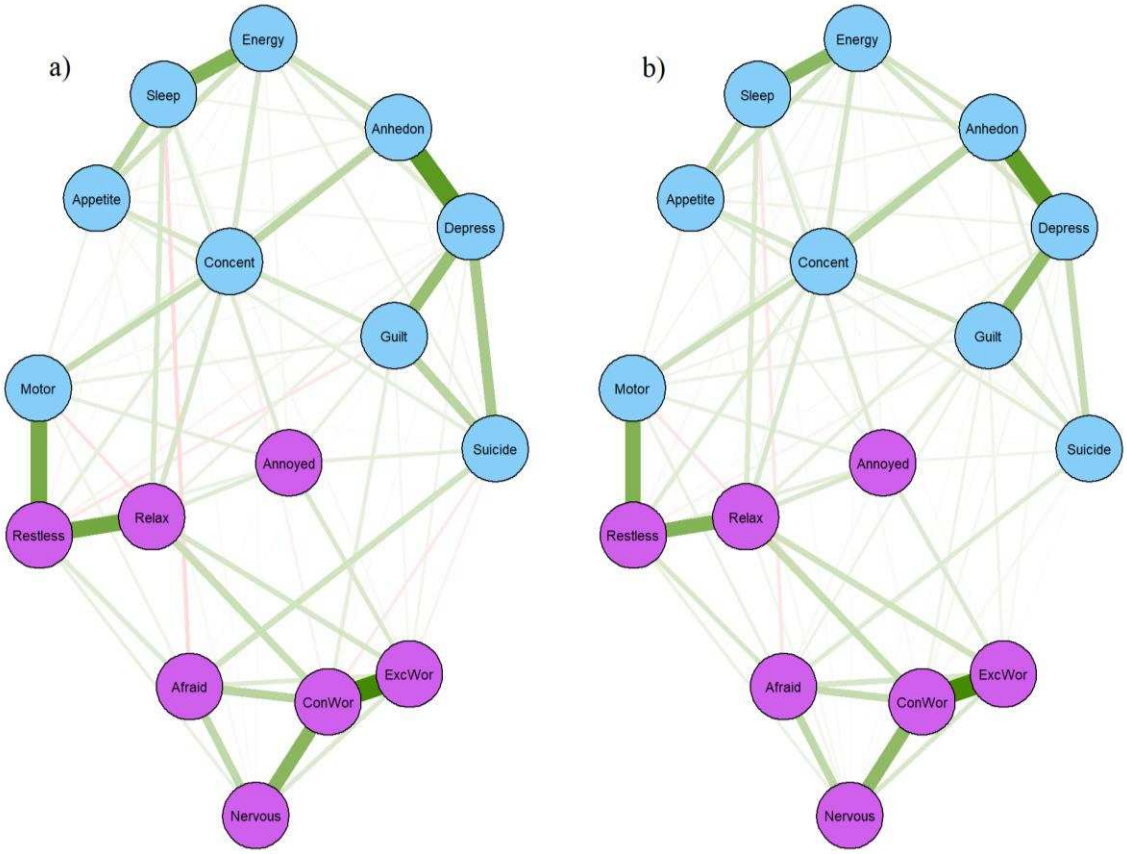

Figure A2. Network of baseline PHQ-9 (blue) and GAD-7 (purple) symptoms for the remission sample using a) polychoric correlations and b) Spearman's correlations

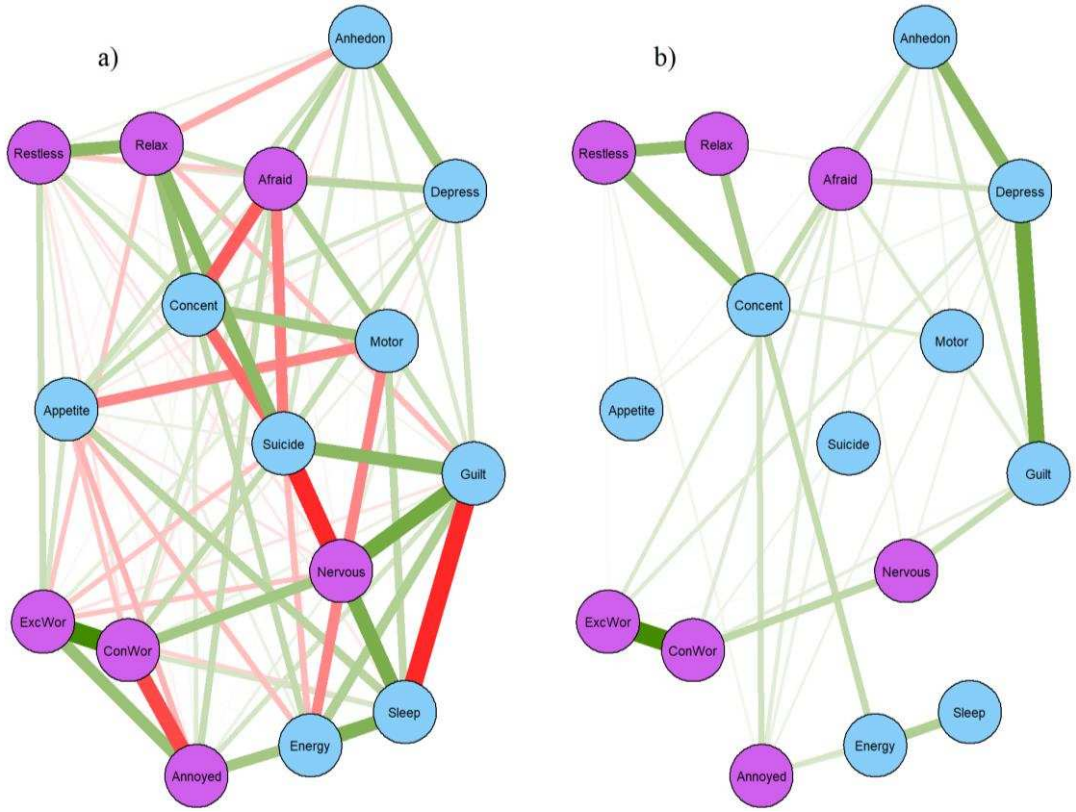

Figure B1. Network of PHQ-9 (blue) and GAD-7 (purple) symptoms at the final treatment session for the relapse sample using a) polychoric correlations and b) Spearman's correlations

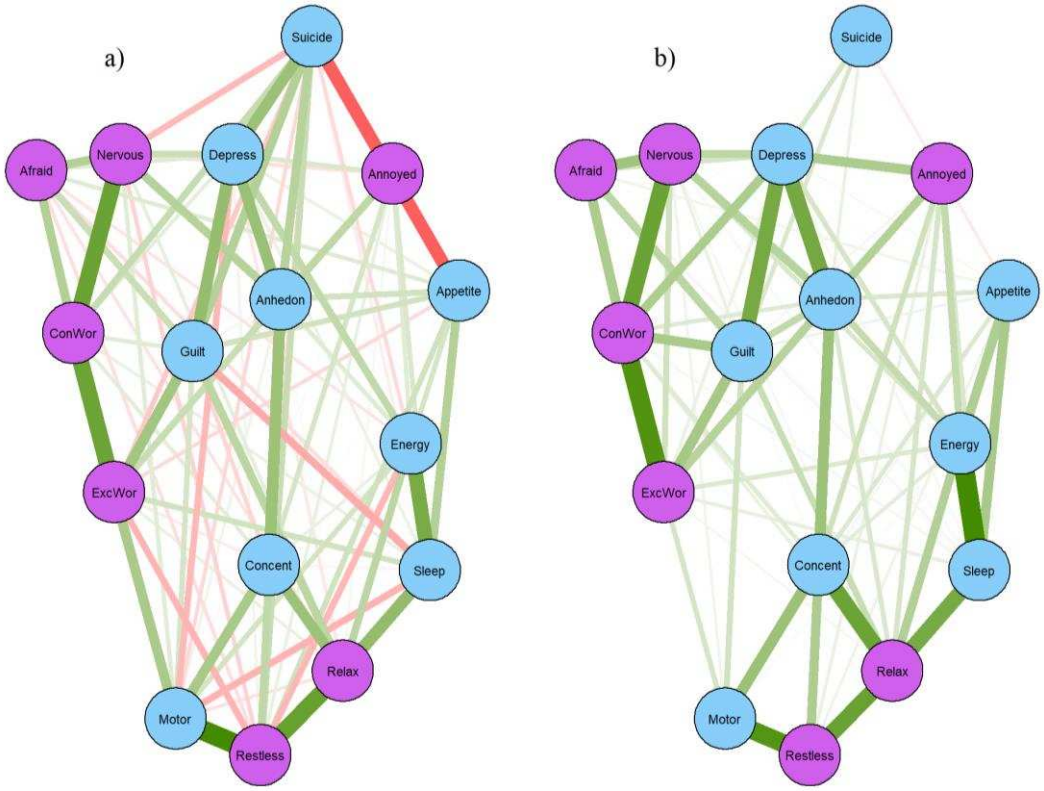

Figure B2. Network of PHQ-9 (blue) and GAD-7 (purple) symptoms at the final treatment session for the remission sample using a) polychoric correlations and b) Spearman's correlations

Table C1

Descriptive Statistics of PHQ-9 and GAD-7 Item Scores for the Relapse Sample at Baseline and at Final Treatment Session

	Baseline Scores		Final Treatment Session Scores	
Item	Range of Scores	Mean Score (SD)	Range of Scores	Mean Score (SD)
PHQ9-Q1	0-3	1.70 (1.06)	0-1	0.40 (0.49)
PHQ9-Q2	0-3	1.93 (0.99)	0-2	0.53 (0.60)
PHQ9-Q3	0-3	2.05 (1.11)	0-3	0.80 (0.85)
PHQ9-Q4	0-3	2.30 (0.93)	0-3	0.83 (0.70)
PHQ9-Q5	0-3	1.37 (1.12)	0-3	0.41 (0.66)
PHQ9-Q6	0-3	1.76 (1.17)	0-3	0.43 (0.62)
PHQ9-Q7	0-3	1.66 (1.20)	0-2	0.40 (0.57)
PHQ9-Q8	0-3	1.00 (1.03)	0-1	0.14 (0.35)
PHQ9-Q9	0-3	0.55 (0.85)	0-1	0.05 (0.23)
GAD7-Q1	0-3	2.30 (0.93)	0-2	0.74 (0.53)
GAD7-Q2	0-3	2.16 (0.96)	0-2	0.52 (0.56)
GAD7-Q3	0-3	2.24 (0.97)	0-2	0.56 (0.54)
GAD7-Q4	0-3	1.97 (1.01)	0-2	0.45 (0.54)
GAD7-Q5	0-3	1.34 (1.11)	0-2	0.25 (0.46)
GAD7-Q6	0-3	1.85 (1.04)	0-3	0.63 (0.67)
GAD7-Q7	0-3	1.56 (1.22)	0-1	0.37 (0.48)

Table C2

Descriptive Statistics of PHQ-9 and GAD-7 Item Scores for the Remission Sample at Baseline and at Final Treatment Session

	Baseline Scores		Final Treatment Session Scores	
Item	Range of Scores	Mean Score (SD)	Range of Scores	Mean Score (SD)
PHQ9-Q1	0-3	1.50 (1.01)	0-2	0.34 (0.49)
PHQ9-Q2	0-3	1.67 (0.97)	0-3	0.45 (0.53)
PHQ9-Q3	0-3	1.94 (1.08)	0-3	0.63 (0.73)
PHQ9-Q4	0-3	1.98 (1.01)	0-3	0.69 (0.68)
PHQ9-Q5	0-3	1.40 (1.15)	0-3	0.33 (0.57)
PHQ9-Q6	0-3	1.71 (1.09)	0-2	0.32 (0.50)
PHQ9-Q7	0-3	1.40 (1.07)	0-3	0.29 (0.49)
PHQ9-Q8	0-3	0.88 (1.02)	0-2	0.11 (0.32)
PHQ9-Q9	0-3	0.43 (0.77)	0-1	0.03 (0.16)
GAD7-Q1	0-3	2.15 (0.93)	0-2	0.64 (0.53)
GAD7-Q2	0-3	2.13 (0.94)	0-2	0.43 (0.51)
GAD7-Q3	0-3	2.14 (0.94)	0-2	0.47 (0.51)
GAD7-Q4	0-3	1.84 (1.00)	0-3	0.39 (0.53)
GAD7-Q5	0-3	1.12 (1.04)	0-2	0.18 (0.40)
GAD7-Q6	0-3	1.64 (1.06)	0-3	0.47 (0.42)
GAD7-Q7	0-3	1.56 (1.13)	0-3	0.30 (0.50)